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# Comprehensive Identification of Pleiotropic Associations for Clonal Haematopoiesis of Indeterminate Potential

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# Hematopoiesis, stem cells and microenvironment

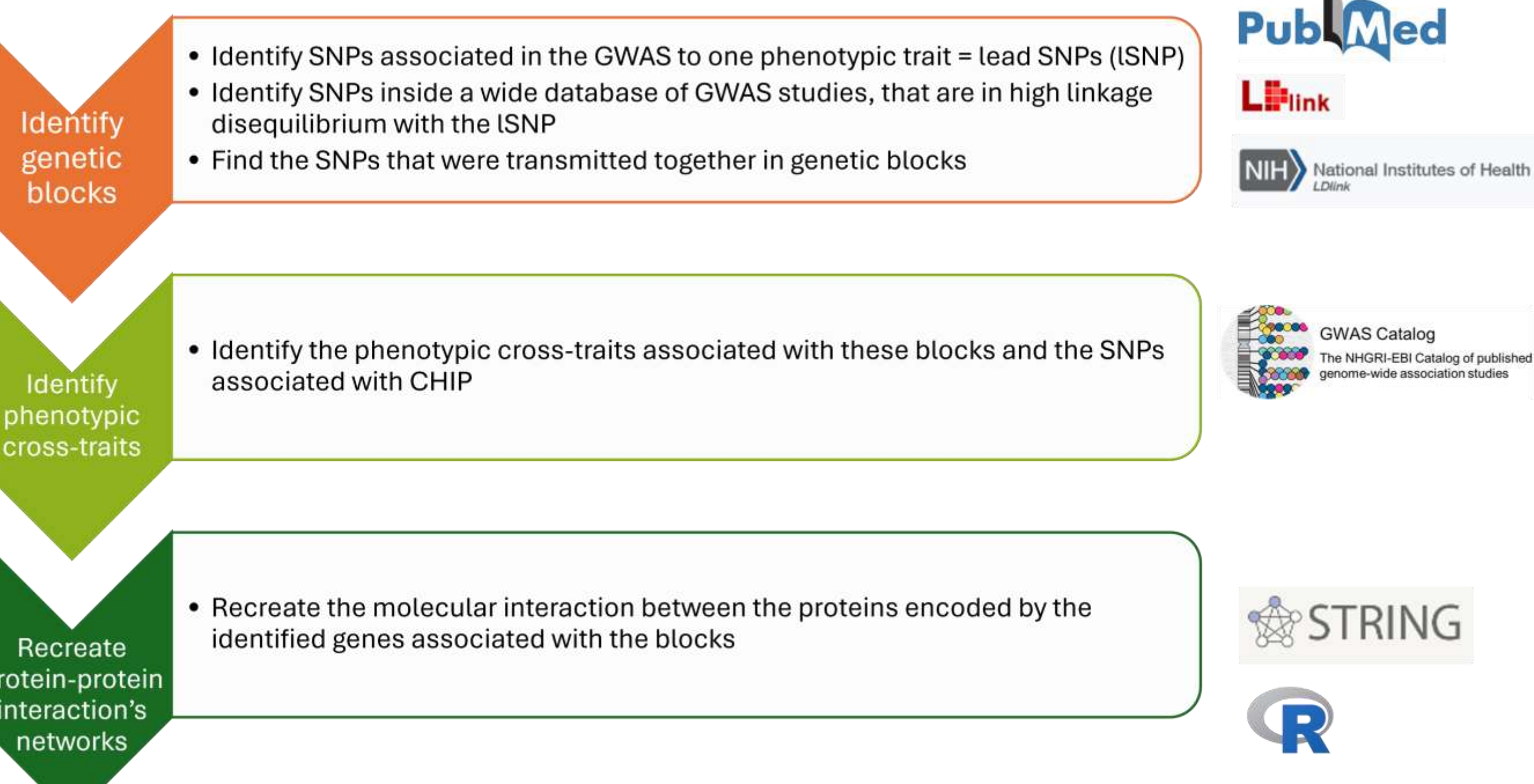
## INTRODUCTION

Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related pre-clinical condition, defined by the presence of driver somatic mutations in leukemia-associated genes occurring in hematopoietic stem cells. It is associated with an increased risk of developing hematologic and non-hematologic disorders including leukemia, solid cancers or cardiovascular diseases<sup>1,2</sup>. Still, knowledge about the inherited and environmental actors shaping CHIP epidemiology is incomplete. Recently, genome wide associations studies (GWAS) have reported several predisposing rare and common variants associated with CHIP across multiple genomic loci, as a background facilitating its emergence<sup>3,4,5,6</sup>.

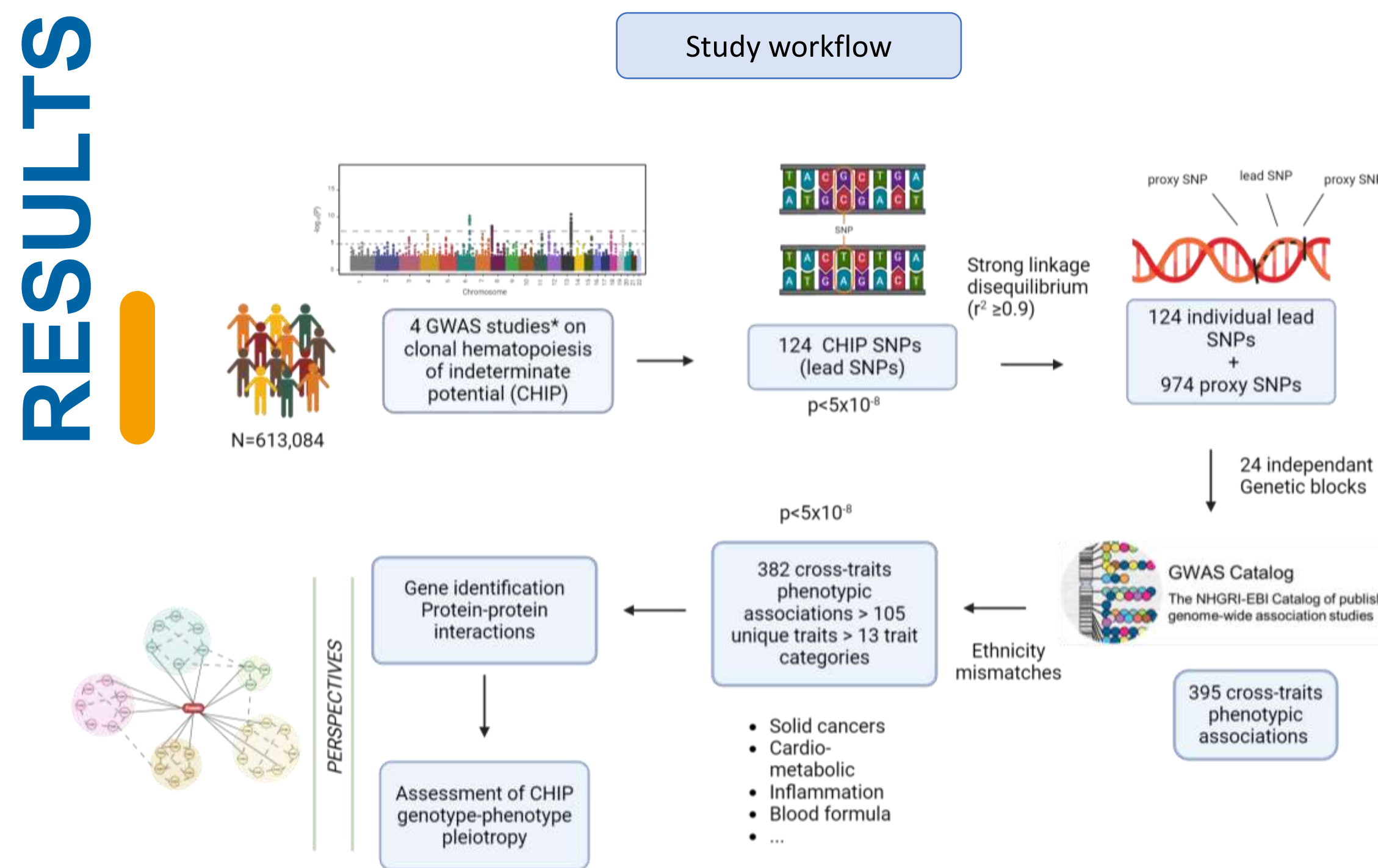
## AIM

Although associations with diverse phenotypes have been reported from epidemiological and mendelian randomization studies, the contribution of all the genotypic features underpinning the spectrum of possible CHIP-associated traits remains poorly explored. Here we catalogued single nucleotide polymorphisms (SNPs) associated with CHIP and explored their pleiotropic potential, phenotype-wise, and their distribution as well as the underlying molecular pathways.

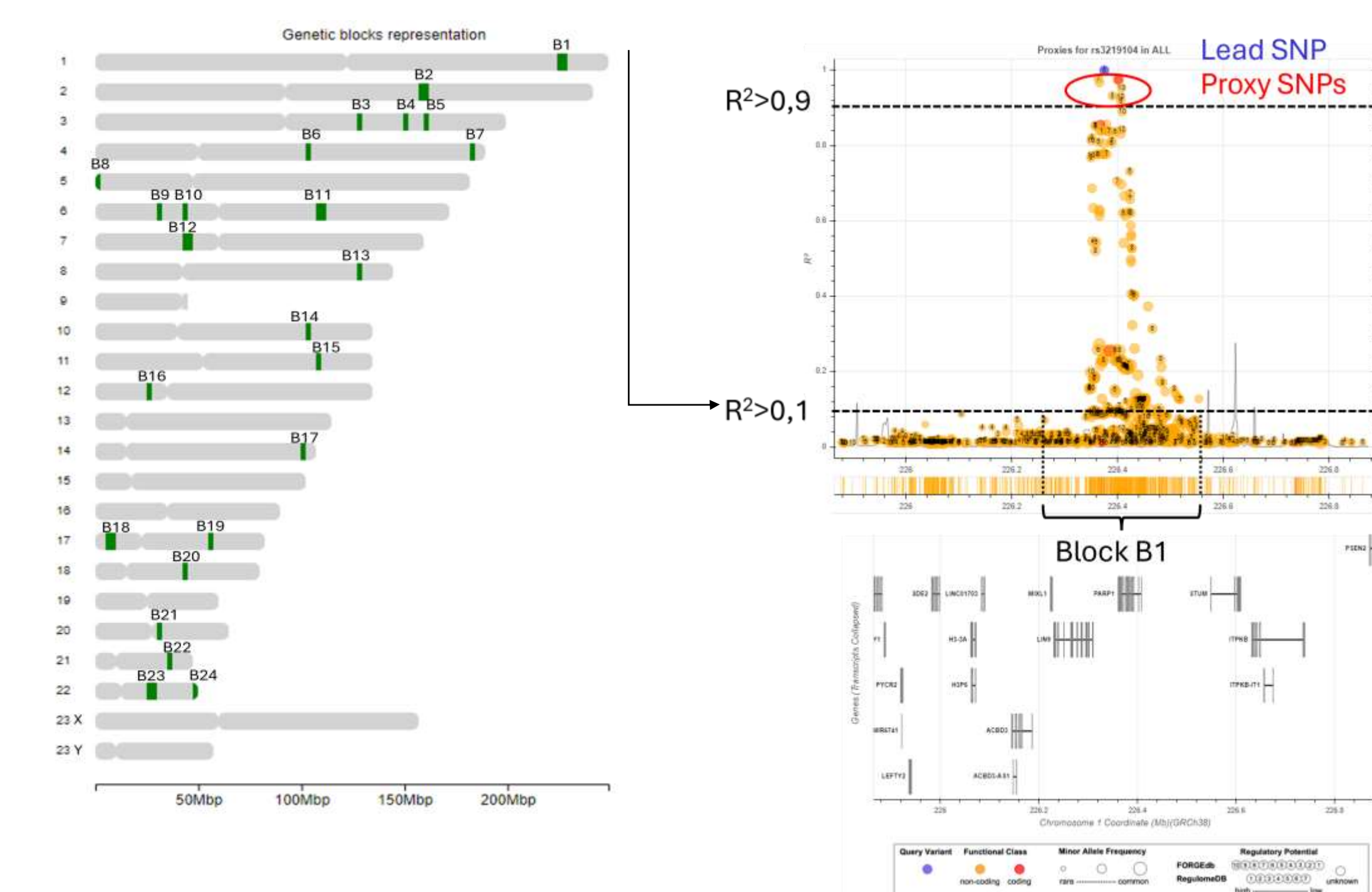
## METHOD



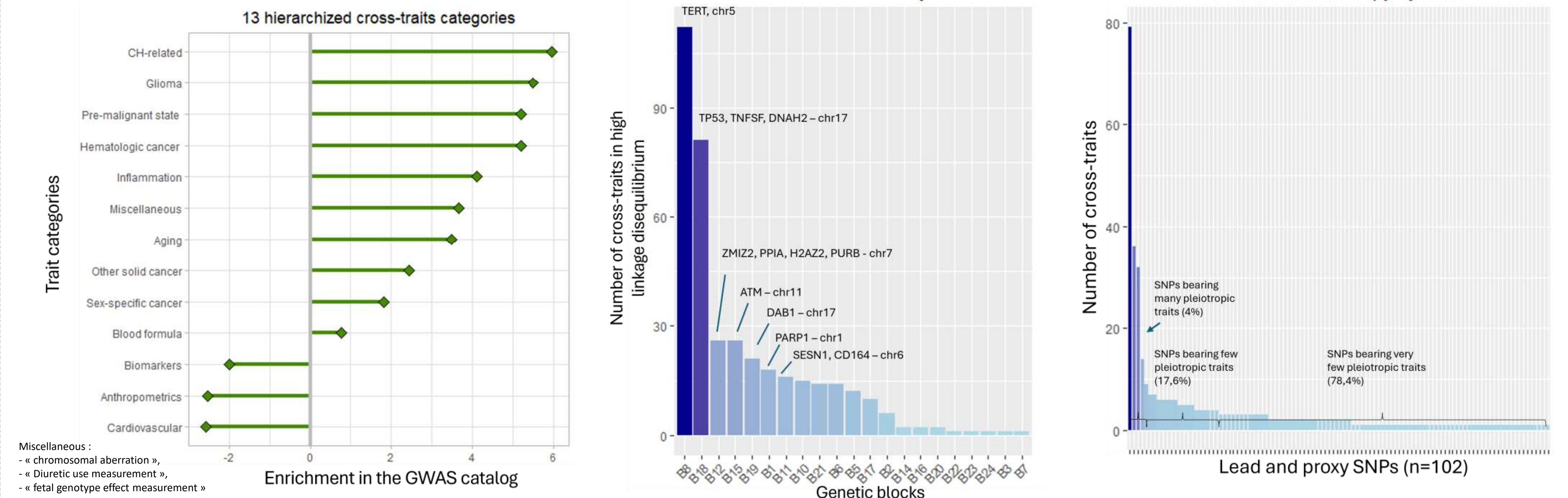
## RESULTS



### 1) Identification of the 24 independent genetic blocks from the 124 individual CHIP lead SNPs.

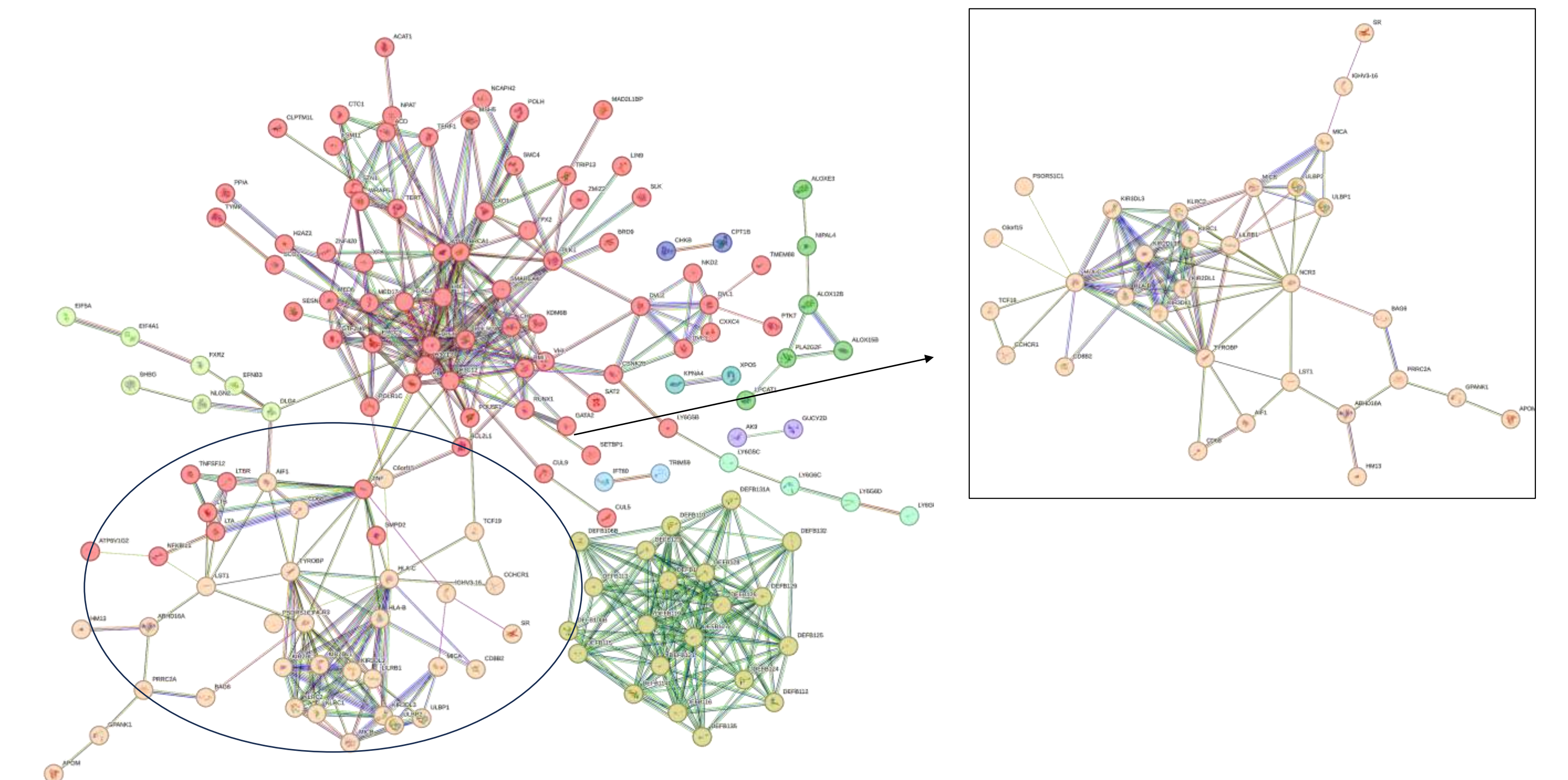


### 2) Identification of cross-traits phenotypic associations and their genomic distribution.



### 3) Overview of the molecular pathways underlying CHIP.

- Protein coding genes located within the 24 genetic blocks are combined with the genes reported as associated with CHIP by the original authors.
- Protein-protein interaction network.
- 9 protein clusters with significantly enriched annotations :
  - Regulation of cell cycle, regulation of telomere maintenance (TP53, TERT, ATM...)
  - Proteins implicated in the innate and adaptive immune system (HLA class I and II, NK cells...)
  - Defensins (probable spurious pleiotropy)
  - Synapse-associated cluster
  - Proteins implicated in lipid metabolism
  - Lymphocyte antigen 6 complex locus proteins
  - Proteins implicated in nucleocytoplasmic carrier activity
  - Proteins implicated in fatty acid beta-oxidation
  - Proteins implicated in purine metabolism



## CONCLUSIONS

- Gene pleiotropy and cross-phenotype genomic distribution in CHIP : an original approach.
- Only a few CHIP genetic blocks are highly pleiotropic. Other positions appear not to be evolutionary conserved.
- Identification of molecular pathways potentially predisposing to CHIP: importance of proteins implicated in the cell cycle, the regulation of telomere maintenance, DNA damage repair, cellular senescence and innate and adaptive immunity.
- Perspectives:**
  - Use of Mendelian Randomization to systematically determine the causal linkage between CHIP and its pleiotropic cross-traits : are these direct or indirect associations and what is the direction of the effect ?
  - Deepen the investigations into the pathways implicated in the immune system in CHIP via PPI network augmentation. Refinement of the PPI network.

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